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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/872,712	06/01/2001	Marina V. Backer	102131-200	4250

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/872,712	BACKER ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,13-17,19-21,27-33,35-37 and 43-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,13-17,19-21,27-33,35-37 and 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *01 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 5/5/04.

Claims 1-3, 5-7, 13-17, 19-21, 27-33, 35-37, and 43-45 remain pending and are under consideration in this Office Action.

Applicant originally elected for examination a species of the invention comprising a carrier molecule (copolymer), a compound (nucleic acids), an adapter (wild type S-protein fragment of bovine RNase A), a targeting ligand (growth factors), and a pharmaceutically acceptable carrier (water). This species was found to be novel and non-obvious in Paper No. 8. In accordance with MPEP 803.02, the Office extended the search to a second combination of species, *i.e.* liposomes, nucleic acids, streptavidin, antibodies, and water which were found to be anticipated by or obvious in view of Bally, (1989), Tillman (1999) or Wickham (1998). Applicant subsequently amended the claims to require that the targeting ligand must be part of a recombinant fusion protein. Each claimed embodiment of this species was found to be obvious or anticipated in the last Office Action. Several species were rejoined in the last Action, including viral particles as carriers, S-protein as an adapter, and VEGF-121 as a targeting ligand. By the last amendment Applicant has limited all claims to require wild type or mutant S-protein of bovine or human ribonuclease A as an adapter, an S-peptide fragment of bovine or human ribonuclease A as a recognition portion of the recombinant targeting fusion protein, and VEGF-121 as a targeting portion of the recombinant targeting fusion protein. It is noted that wild type" and "mutant" S-proteins were considered to be distinct species in the original restriction requirement. As such, Applicant's amendment includes two distinct species. The Office selects "wild type S-protein of bovine or human ribonuclease A" for examination. There are two species of invention under

consideration in this Office Action, one in which the delivery vehicle is a viral particle, and one in which the delivery vehicle is a liposome. The other elected elements in each species of delivery vehicle are: nucleic acids as a compound for delivery; wild type S-protein as an adapter; and VEGF 121 as the targeting portion of the targeting fusion protein.

Rejections Withdrawn

The rejection of claims 8, 11, 22, 25, 38, 41, 64, 65, 74, and 75 are rejected under 35 U.S.C. 112, first paragraph for new matter is withdrawn in view of Applicant's amendments.

The rejection of claim 30 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendment.

All previous rejections under 35 USC 102 and 103 are withdrawn in favor of the following rejections necessitated by Applicant's amendments.

Objections Withdrawn

The objection to the specification over introduction of new matter is withdrawn in view of Applicant's amendment.

Claim Objections

Claims 6, 20, and 36 are objected to because "anhydrdride" and "polyethyleneglycoles" are misspelled. See e.g. lines 5 and 8 of claim 6.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-7, 13-17, 19-21, 27-33, 35-37, and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valerio et al (WO 97/05266, published 2/13/97), Allen et al (US 2001/038851, published 11/8/01), Tischer et al (US 5,194,596, issued 3/16/93), and Theodore et al (US Patent 6,075,010, issued 6/13/00).

Valerio teaches a method of producing gene delivery vehicles which can be transferred to pre-selected cell types in vivo by using targeting conjugates. The gene delivery vehicles comprise: 1) the gene of interest; and 2) a viral capsid or envelope carrying a member of a specific binding pair, the counterpart of which is not directly associated with the surface of the target cell. The targeting conjugates are composed of the counterpart member of the specific binding pair linked to a targeting moiety which is a cell-type specific ligand. See abstract. The first member of the binding pair may be covalently attached to the carrier e.g. as a fusion to a capsid protein. See paragraph bridging columns 8 and 9. The targeting conjugate may be a fusion protein. See page 9, lines 14-23. See also page 16, lines 8-27. In terms of the instantly claimed invention, the virus of

Valerio corresponds to the carrier, the first member of the specific binding pair corresponds to the adapter, the second member of the binding pair corresponds to the recognition portion of the targeting fusion protein, and the targeting moiety corresponds to the targeting portion of the targeting fusion protein.

Valerio does not teach the use of VEGF 121 as a targeting moiety in the targeting conjugate, or the use of S protein and S-peptide as a binding pair. More specifically, Valerio does not teach the use of S protein as an adapter and the use of S-peptide as a recognition moiety in a targeting fusion protein.

Allen teaches that VEGF can be used as a targeting moiety in delivery complexes.

Tischer teaches that VEGF 121 is an art recognized equivalent of VEGF in terms of its function in wound healing. See column 3, line 67 to column 4, line 9, Fig, 7, and column 10, lines 63-68. Clearly this function entails binding its receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use VEGF 121 as a targeting moiety in a fusion targeting construct of Valerio. One would have been motivated to do so because Valerio teaches that ligands that recognize cellular receptors should be used as targeting moieties in targeting conjugates, and because Allen teaches that VEGF is a useful targeting ligand in the context of delivery vehicles. It would have been obvious to use VEGF 121 as a targeting ligand because it is an art recognized variant of VEGF. See Tischer above. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the

other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the essential function and intended use of VEGF/VEGF 121 is to recognize and bind to the receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Valerio, Allen, and Tischer by using the S-protein and S-peptide binding pair of Theodore. One would have been motivated to do so because Theodore indicates that this binding pair is equivalent to other binding pairs such as the biotin-streptavidin binding pair taught by Valerio.

With regard to claims 5, 19, and 35, the viral carrier of Valerio comprises a variety of capsid proteins that can be considered to be polymers comprised by the carrier.

Thus the invention as a whole was *prima facie* obvious.

Claims 1-3, 5-7, 13-17, 19-21, 27-33, 35-37, and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bally et al (US Patent 4,885, 172, issued 12/5/1989), Valerio et al (WO 97/05266, published 2/13/97), Allen et al

(US 2001/038851, published 11/8/01), Tischer et al (US 5,194,596, issued 3/16/93), and Theodore et al (US Patent 6,075,010, issued 6/13/00).

Bally teaches a composition and methods for delivering bioactive materials comprising a liposomal carrier, wherein the lipids are covalently modified with the adapter streptavidin, and biotinylated targeting antibodies are then bound to the adapter. See abstract. In one embodiment, the bioactive material is the chemotherapeutic reagent doxorubicin. See column 3, lines 36-41. In another embodiment the bioactive material is a polynucleotide. See column 6, lines 24 and 25. The antibodies recognize cell surface antigens. See e.g. column 4, lines 15-17. The compositions are delivered in an aqueous solution, as required by instant claim 45. See column 9, lines 51-54.

Bally does not teach the use of VEGF 121 as a targeting moiety, or the use of S protein and S-peptide as a binding pair. More specifically, Valerio does not teach the use of S protein as an adapter, or a targeting fusion protein comprising S-peptide as a recognition moiety and VEGF 121 as a targeting moiety.

The teachings of Valerio, Allen, Tischer , and Theodore are discussed above. Valerio teaches a method of producing gene delivery vehicles which can be transferred to pre-selected cell types by using targeting conjugates. The gene delivery vehicles comprise: 1) the gene of interest; and 2) a viral capsid or envelope carrying a member of a specific binding pair, the counterpart of which is not directly associated with the surface of the target cell. The targeting conjugates are composed of the counterpart member of the specific binding pair

linked to a targeting moiety which is a cell-type specific ligand. See abstract. The first member of the binding pair may be covalently attached to the carrier e.g. as a fusion to a capsid protein. See paragraph bridging columns 8 and 9. The targeting conjugate may be a fusion protein. See page 9, lines 14-23. See also page 16, lines 8-27. In terms of the instantly claimed invention, the virus of Valerio corresponds to the carrier, the first member of the specific binding pair corresponds to the adapter, the second member of the binding pair corresponds to the recognition portion of the targeting fusion protein, and the targeting moiety corresponds to the targeting portion of the targeting fusion protein.

In light of the teachings of Allen, Tischer, and Theodore, it would be obvious to use VEGF 121 as a targeting moiety, and S-protein and S-peptide as a binding pair in the invention of Valerio, as discussed in the preceding rejection.

It would have been obvious to covalently modify the liposomes of Bally with S protein and to use the recombinant fusion targeting protein described above to target these liposomes. One would have been motivated to do so because Theodore teaches that the S protein-S peptide binding pair is equivalent to other binding pairs such as the biotin streptavidin binding pair taught by both Bally and Valerio. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that

the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Further one would have been motivated to use the recombinant fusion polypeptide rendered obvious by Valerio, Allen, Tischer, and Theodore as a targeting ligand because it is easily produced by recombinant means, easily purified, and requires no further covalent modification such as a biotinylation step.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 5/5/04 have been fully considered to the extent that they apply to the rejections set forth above, but they are not persuasive.

Applicant's argument pertinent to the standing rejections are set forth at pages 24-26. Applicant argues at page 25 that none of the cited references taken individually or in combination teaches a molecular delivery vehicle comprising an adapter comprising a wild type S-protein fragment of bovine or human ribonuclease A in combination with a recombinant targeting fusion protein comprising a recognition portion and a targeting portion, wherein the recognition portion consists essentially of a recognition peptide comprising S-peptide from bovine or human ribonuclease A, and the targeting portion comprises VEGF 121.

Specifically, while Applicant admits that Valerio teaches recombinant fusion proteins comprising a targeting conjugates, Applicant asserts that these

are discussed in the context of leucine zipper terminal domains, and asserts that there is no disclosure related to a recombinant product comprising S-peptide in Valerio or any of the other cited references. This is unpersuasive because Valerio teaches at the paragraph bridging pages 14 and 15 that in one embodiment "the member of the specific binding pair and its counterpart are both peptides forming three-dimensional structures that can interact in solution. Peptides useful in this aspect of the invention include but are not restricted to dimerization motifs that are identified within proteins known to form dimers, such as the yeast transcription factor GCN4, the mammalian transcription factor C/EBP, and the nuclear transforming oncogene products fos, jun, and myc." Clearly, Valerio envision as a useful binding pair any pair of peptides that form three-dimensional structures that can interact in solution. Theodore teaches that S-protein and S-peptide are well known members of this genus. Valerio's exemplification of leucine zippers does not limit what the disclosure fairly teaches only to leucine zippers. Instead one of ordinary skill in the art, aware of the teachings of Theodore regarding binding pairs, would have been motivated to use S-peptide and S-protein appropriately in the invention of Valerio because it was clear that they would function equivalently to other binding pairs such as biotin and streptavidin.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Richard Schnizer, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER